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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/438,358	11/12/1999	Gary F. GERARD	0942.4640001	9194

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STERNE, KESSLER, GOLDSTEIN & FOX PLLC
1100 NEW YORK AVENUE, N.W., SUITE 600
WASHINGTON, DC 20005-3934

EXAMINER	
LEFFERS JR, GERALD G	

ART UNIT	PAPER NUMBER
1636	21

DATE MAILED: 11/19/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/438,358	Applicant(s) GERARD ET AL.	
	Examiner Gerald G Leffers Jr.	Art Unit 1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 September 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14-51,65-76 and 81-104* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14-51,65-76 and 81-104* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *19, 21* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A proper request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9/3/02 as Paper No. 24 has been entered.

The amendment filed as Paper No. 24 comprises cancellation of several claims (claims 77-80), amendment of several claims (claims 14, 18-19, 31, 40), and adds several new claims (claims 89-104). Claims 14-51, 65-76 and 81-104 are pending in this application and are under consideration.

Any rejection of record in the previous office actions that is not addressed in this action is withdrawn. This action is not final.

Information Disclosure Statement

Receipt is acknowledged of information disclosure statements filed 8/1/02 and 9/3/02 (Paper Nos. 19 and 21, respectively). The corresponding PTO Form 1449 has been mailed along with this action.

It is noted that applicants have requested in Paper No. 24 that a PTO Form 1449 corresponding to references listed on the IDS filed 9/18/00 as Paper No. 7, but not considered at that time because they were not present in the file, be mailed to applicant. Applicants assert (in

VII. Other Matters, page 20, Paper No. 24) that the additional references were mailed along with other references submitted with the IDS filed 3/8/01 as Paper No. 10. It is further asserted that a PTO Form 1449 corresponding to those references was also filed with Paper No. 10. Although the transmittal form for Paper No. 10 indicates the missing references were mailed to the Office, neither the references nor the corresponding PTO Form 1449 are present in the file. If applicant wishes these references to be considered, it will be necessary to send in a PTO Form 1449 corresponding to the references as well as additional copies of the references.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 89-91, 97-101 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 89-91, 97-101 each comprise the limitation of "...at least one isolated ____ protein..." where the protein is an IHF, Cre, Xis, Int, FIS, etc. There is no literal support for these limitations in the specification as originally filed. Therefore, these limitations are impermissible NEW MATTER.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 14-51, 65-76 and 81-104 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 14-51, 65-76 and 81-104 are vague and indefinite in that they cite the limitation that the ribosomal proteins added to the recombination mixture are "purified". The metes and bounds of this term are important in that applicants are attempting to use this term to delineate the instant claims from the prior art where crude cell extracts are used to supply the recombinase proteins and which would also necessarily comprise one or more ribosomal proteins. While the specification describes the purification of different ribosomal proteins from cells, it does not provide an explicit definition as to when in the process proteins are considered to be "purified". It would be remedial to amend the claim language to clearly indicate to what extent the ribosomal proteins of the inventions have to be isolated from their environment in order to satisfy the limitation of being "purified".

Claims 102-103 are vague and indefinite in that there is no clear and positive prior antecedent basis in claims 31 and 40, upon which claims 102-103 are dependent, for the words "said first or second nucleic acid molecule".

Claim 104 is vague and indefinite in that there is no clear and positive prior antecedent basis for the words "said fourth nucleic acid molecule" in claims 14, 19, 31 and 40. These are independent claims upon which claim 104 is directly dependent.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 31-32, 36, 38-51, 65-72, 74-76, 87-89, 91-95, 98 and 100-103 are rejected under 35 U.S.C. 102(b) as being anticipated by Nash (Methods in Enzymology. Vol. 100, pp210-216, see the entire reference). **This rejection is maintained for reasons of record in the previous Office actions (Paper Nos. 8 and 13). This rejection is extended to new claims 89, 91-95, 98 and 100-103.**

It is noted that Nash teaches the "isolation" of ribosomal and recombinase proteins to varying degrees for use in the recombination reaction mixtures throughout the reference. Nash also teaches the recombinant expression of the recombinase Int (e.g. pages 212-213, *Purification*). The newly added claim limitations regarding addition of BSA, spermidine, etc., to the reaction mixture can be found in the Materials and Methods section of Nash.

Claims 40-51, 89-103 are rejected under 35 U.S.C. 102(b) as being anticipated by Abremski et al (V; The Journal of Biological Chemistry, Vol. 259, No. 3, pages 1509-1514; see the entire reference) and Abremski et al (W; The Journal of Biological Chemistry. Vol. 257, No. 16, pages 9658-9662; see the entire reference). **This rejection is maintained for reasons of record in the previous Office actions (Paper Nos. 8 and 13). The rejection is extended to new claims 89-103.**

This rejection is maintained for reasons of record in Paper No. 8, mailed 11/8/00 and extended to newly added claims 80 and 88.

It is noted both references teach the "isolation" of ribosomal and recombinase proteins to varying degrees for use in recombination reaction mixtures. Both references teach the recombinant expression of recombinase proteins.

Response to Arguments/35 U.S.C 102 Rejections

Applicant's arguments filed in Paper No. 24 have been fully considered but they are not persuasive. Applicants' response incorporates by reference each of the arguments against these grounds of rejection previously put forth in Paper No. 12. Applicants' amendment in Paper No. 24 includes the incorporation of the limitation of "purified" ribosomal proteins that are added to the in vitro recombination mixture for each of the rejected claims. Paper No. 24 essentially argues: 1) the examiner's interpretation of the word "isolation" differs from that which has been defined, interpreted and often used by those of ordinary skill in the art in reference to the isolation of proteins, 2) the ribosomal proteins present in the crude extracts taught by the cited prior art are not "set apart from others" or "pure or in a free state", 3) applicants do not agree that the crude extracts taught by the cited prior art would necessarily comprise ribosomal proteins, and 4) the examiner has assumed that it is *possible* that the ribosomal proteins are present in the crude extracts and that inherency cannot be established by mere probabilities or possibilities.

It is noted that applicants have indicated that they consider the terms "isolated" and "purified" to be synonymous (page 13, bottom paragraph, Paper No. 24). Neither applicants' specification nor the definition provided in Paper No. 24 distinguish the instant claims from the

methods taught in the prior art. In the biochemical arts the terms "isolated" and "purified" are subjective terms when applied to proteins, encompassing a crude level of purification (e.g. centrifuged cell lysates) to highly pure preparations of protein that are essentially homogenous (e.g. >99 % purified from contaminating cell products). The definition provided by applicants' response does not set where on this continuum one would consider a protein to be "purified". How separated from other cellular proteins does the ribosomal protein of the invention have to be in order to be considered "pure", "isolated" or "in a free state"? Does the ribosomal protein have to constitute 25% of the total protein in a mixture in order to be "purified"? 75%? There is no basis in the specification or in the definition provided in applicants' response to indicate where one would draw the line. Therefore, the limitation of "purified" ribosomal protein cannot be considered as delineating the claimed invention from the cited prior art.

With regard to the argument that the examiner is improperly basing the inherency argument on mere probabilities or possibilities, the examiner has presented a reasoned argument for why it necessarily flows from the teachings of the prior art that ribosomal proteins would necessarily have been present in the crude extracts of the prior art. The response only addresses part of this rational, leaving out the supporting evidence cited by the examiner in support of the inherency argument. The rational is as follows.

The Nash et al reference teaches that the crude E. coli cell extracts utilized for characterization of the λ int recombinase were generated by lysis of the cell wall/membrane by sonication and centrifugation at 15,000 RPM for 20 minutes to pellet the insoluble debris (e.g. page 212, second full paragraph, *Preparation of crude IHF*). Both of the Abremski et al references teach lysis of E. coli cells by sonication and centrifugation at 17,000 RPM for 30 minutes to generate crude extracts which were assayed for recombinase activity (e.g. see each results section under *Enzyme Purification*). Such cell lysis and centrifugation techniques are and were routinely practiced in the art and are recognized as providing an E. coli cell extract comprising isolated and soluble proteins, including ribosomal polypeptides. For example, Robyt and White teach that a centrifugal force of up to 100,000g for 3-10 hours is required to sediment ribosomal proteins (Table 8-2; *Biochemical Techniques-Theories and Practice*, John F. Robyt and Bernard J. White, 1987, Brooks-Cole publishers, Monteray CA). The examiner knows of no commonly used centrifuge rotor that will generate these kinds of centrifugal forces at the speeds indicated by the supporting references.

The response of Paper No. 24 provides no evidence for any centrifuge rotor that would generate the necessary G-force to sediment the E. coli ribosomal proteins under the experimental conditions taught in the cited references.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 14-51, 65-104 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hartley et al in view of Nash (U) or Abremski et al (V) or Abremski et al(W). **This rejection is maintained for reasons of record in Paper Nos. 8 & 13. This rejection is extended to newly added claims 89-104.**

Response to Arguments

Applicant's arguments filed in Paper No. 24 have been fully considered but they are not persuasive. Applicants' response essentially argues: 1) the examiner acknowledges that Hartley et al does not disclose or contemplate the specific limitation of using purified ribosomal proteins, 2) it is unclear why the examiner contends that the methods taught by Hartley "encompass" in vitro methods using cellular extracts, 3) a general teaching cannot be a basis of a prima facie case of obviousness, 4) the examiner insinuates that crude extracts would inherently contain ribosomal proteins because the crude extracts contain other cellular factors which can aid in recombination, 5) there is no such thing as "inherent obviousness" since inherence and obviousness are different legal concepts (i.e. "Obviousness cannot be predicated on what is unknown."), 6) the examiner has not provided evidence to suggest why one of ordinary skill in the art would specifically use isolated or purified ribosomal proteins to aid in recombination, 7) the examiner is reminded that the motivation to combine must come from the references themselves or from general knowledge in the art, 8) the examiner has not examined the claim as a whole and is required to determine whether the prior art suggests the claim as a whole (i.e. the examiner has alleged that crude extracts can be used in place of purified ribosomal proteins in the reaction mixture), and 9) the examiner has failed to provide evidence as to why one of ordinary skill in the art would have preferred purified ribosomal proteins over the crude extracts as disclosed by the cited prior art.

With regard to the teachings of Hartley et al, it is and has been conceded that the patent does not teach the use of crude extracts. However, with regard to whether the teachings of Hartley et al embrace the use of crude extracts for in vitro recombination reactions, one of

ordinary skill in the art would necessarily understand that in vitro embodiments of the invention would include the use of crude extracts because 1) Hartley et al don't teach that such extracts cannot be used in their methods, and 2) the use of crude extracts was commonly known in the art as evidenced by the teachings of the supporting references.

With regard to a general teaching being the basis for a prima facie case of obviousness or the statement that there is no such thing as "inherent obviousness", these arguments appear to be based on the assumption that the examiner has based his motivation to combine the cited references on the inherent presence of the ribosomal proteins in the crude extracts taught by Nash or the Abremski et al references. This assumption is not accurate. The presence of the ribosomal proteins has nothing to do with the motivation supplied by the examiner. The motivation cited in rejecting these claims was that one would have been motivated to do so in order to provide the recombinase proteins and associated host cell factors (e.g. IHF, etc.) in a rapid manner without the need for further purification of the proteins. Such motivation is known in the art, as evidenced in part by the teachings of the Nash and Abremski et al references.

With regard to arguments based upon the purported difference between the cited prior art and the limitations "isolated" or "purified", these arguments have been dealt with above. To summarize, the examiner contends that these limitations do not distinguish the instant claims over the prior art. With regard to the allegation that the examiner has not examined the claim as a whole, the examiner has provided evidence and arguments to support rejection of the claims based upon every limitation present in the pending claims, including the terms "isolated" and "purified".

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 14-51, 65-88 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 29-37 of U.S. Patent No. 5,888,732. Although the conflicting claims are not identical, they are not patentably distinct from each other for reasons of record in Paper Nos. 8 and 13. **This rejection is maintained for reasons of record in Paper Nos. 8 and 13.**

Response to Arguments

Applicant's arguments filed in Paper No. 12 have been fully considered but they are not persuasive. Applicants' response to the Obviousness Double Patenting rejection merely reiterates the arguments presented above against rejection of the instant claims as obvious over Hartley et al in view of Nash or the Abremski et al references. These arguments have been dealt with above.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gerald G Leffers Jr. whose telephone number is (703) 308-6232. The examiner can normally be reached on 9:30am-6:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on (703) 305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-7939 for regular communications and (703) 305-7939 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Gerald G Leffers Jr.
Examiner
Art Unit 1636

Ggl
November 18, 2002